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ANACIN AND OTHER PHENACETIN COMBINATION DRUGS

Anacin (Whitehall), a combination of 3 grains of phenacetin with 3.25 grains of aspirin and 0.235 grains of caffeine, is perhaps the most heavily promoted drug on the TV networks. It is also promoted in medical journals as "better than aspirin" for headaches, musculo-skeletal aches, "neuralgia," and "neuritis." Other combination drugs containing phenacetin, aspirin and caffeine are: APC (many companies), Empirin Compound (Burroughs Wellcome), ASA Compound (Lilly), Acetidine (Merck), Aspirofeine (McNeil), PAC Compound (Upjohn), and Stanback (Stanback Co.). Phenacetin (or acetophenetidin), alone and in combination with other drugs, has been used liberally as an analgesic and antipyretic since its introduction into medical practice in 1887, and it has generally been considered a relatively safe drug (P. K. Smith, Acetophenetidin, Interscience Publishers, 1958). Questions about its safety are, however, being raised with increasing frequency.

TOXIC EFFECTS - Despite the difficulty of distinguishing the effects of acetophenetidin from those of other drugs given simultaneously, it is clear that doses of a gram or more taken daily for months or years have occasionally caused methemoglobinemia, sulfhemoglobinemia and hemolytic anemia. Recent clinical and pathological studies also indicate that excessive use of phenacetin can cause severe renal injury (chronic interstitial nephritis with papillary necrosis). Though the evidence is circumstantial, it would seem prudent for physicians and dentists to restrict refill privileges on phenacetin prescriptions, and for the Food and Drug Administration to require label warnings of potential blood and renal injury from excessive use of over-the-counter drugs containing phenacetin.

Methemoglobinemia, sulfhemoglobinemia, shortened red-blood-cell survival time, and hemolytic anemia, the chief toxic effects of prolonged use of large doses of phenacetin, are most likely to occur in the presence of concurrent disease, especially renal disease (T. Friis, et al., Acta Medica Scandinavica, 167:253, 1960). A recent report (B. H. MacGibbon, et al., Lancet, 1:7, 1960) indicates that red blood cells with adsorbed phenacetin can act as antigens, producing autoantibodies and leading to acute hemolytic anemia and acute renal failure, but such hypersensitivity reactions are probably uncommon. Of greater concern is the fact that since 1953 many reports have appeared in the Swiss, Scandinavian and German medical literature, and there has been one American report (S. E.

Moolten and I. B. Smith, Am. J. Med., 28:127, 1960) attributing chronic interstitial nephritis with necrotizing papillitis and severe tubular degeneration to excessive use of phenacetin; the disease develops insidiously, and the effects are often irreversible and sometimes fatal.

AMOUNT USED - One gram or more of phenacetin taken daily for prolonged periods is the amount reported to cause renal damage, and one gram is the amount present in the maximum recommended daily doses of most of the over-the-counter preparations. Most of the preparations carry no label warnings against prolonged use; in view of the nature of the promotion for many of these products and the kind and chronicity of the ailments for which they are recommended, excessive and prolonged use by many persons must be assumed. The amount of phenacetin sold in this country in a year, according to the best available estimates, would be the equivalent of about three billion one-gram doses, or enough to provide a gram a day for about eight million persons.

Controlled clinical studies on the comparative analgesic effects of aspirin and phenacetin are lacking, but in the opinion of Medical Letter consultants, phenacetin has no analgesic or antipyretic superiority over aspirin. A review of the uncontrolled studies (cited by P. K. Smith, above) indicates that equal milligram doses of these drugs appear to have equal analgesic effect on headache and musculo-skeletal pains, and approximately equal antipyretic effect. There is no convincing evidence that phenacetin has significant sedative action, as claimed by the makers of Anacin.

EFFECT OF COMBINATION - The widely held assumption that the combination of phenacetin, aspirin and caffeine has greater analgesic effectiveness than the equivalent dose of aspirin alone has never been supported by carefully controlled trials. On the basis of the evidence that is available, it seems clear that an equivalent dose of aspirin will relieve pain as effectively as the phenacetin-aspirin-caffeine combination. The continued use of large amounts of aspirin unquestionably has its risks (such as erosive gastritis from undissolved residues, and hypoprothrombinemia), but in view of the possibility of renal and blood damage from prolonged use of large doses of phenacetin, aspirin is probably safer for long-term use.

Experiments with human subjects suggest the possibility that a contaminant, acetic-4-chloranilide, present in varying amounts in both European and American phenacetin, may be largely responsible for the renal injury (B. Harvald, et al., Lancet, 1:303, 1960) and methemoglobinemia (I. Gad, et al., Ugeskrift Laeger, 112:1405, 1950) associated with the use of phenacetin drugs. If it should be established that the contaminant is responsible for all or most of the toxic effects of the drug, and if it can be eliminated, the entire picture may change.

For the present, physicians should not encourage the use of phenacetin (except by patients hypersensitive to aspirin), and labels on over-the-counter products containing the drug should give clear and emphatic warnings against excessive use. Renal disease should be considered a contraindication to anything more than brief use of small doses of phenacetin.

THROMBOLYSIN

A Medical Letter evaluation of Actase (Ortho), a preparation of "fibrinolysin" (1:93, Dec. 11, 1959), indicated that contrary to the manufacturer's claims, this preparation had no proved effect on intravascular thrombi. Recent studies confirm this evaluation and show that Actase lacks significant thrombolytic effect even in vitro (A. P. Fletcher, et al., JAMA, 172:912, 1960; D. L. Watt and R. L. MacMillan, Canad. Med. Assn. J., 83:1436, 1960).

Thrombolysin (Merck) is a new "fibrinolysin" preparation. Both Actase and Thrombolysin are described by their manufacturers as containing 50,000 units of fibrinolysin (plasmin) per vial. In vitro assays, however, showed 20 times as much plasmin in Thrombolysin as in Actase (A. P. Fletcher, et al., J. Lab. Clin. Med., in press). Though both preparations are designated as human "fibrinolysin," whatever thrombolytic effect they have may be due mainly to the streptokinase present in both. The Fletcher studies showed much more streptokinase in Thrombolysin than in Actase. Some investigators believe that the recommended dose of Thrombolysin – four vials or more per day – can produce an active thrombolytic state in some patients. On the basis of his experience with the drug, however, one Medical Letter consultant believes that Thrombolysin is likely to have significant value in thrombophlebitis only in doses of about 10 vials or more per day.

While the experimental and clinical evidence suggests that Thrombolysin may have some value in thrombophlebitis, the preparation has not been proved to be useful in coronary artery disease, strokes, pulmonary embolism or other major thromboembolic disorders. It is not likely that the use of thrombolytic agents for lysing intravascular clots will become practical until many problems of choice, preparation and standardization of agents, elimination of pyrogens, and the establishment of simple laboratory guides for controlling therapy are solved. Until a safe and not too costly thrombolytic agent, with effectiveness proved by controlled trials, becomes available, primary reliance in thromboembolic diseases must be on anticoagulant drugs. If Thrombolysin is tried, the manufacturer's cautions and contraindications should be carefully noted. The cost of Thrombolysin to the physician is about $30 per 50,000-unit vial, or about $300 for 10 vials.

PREMARIN AND CORONARY ARTERY DISEASE

The claim that Premarin (conjugated estrogenic substances, USP) "can definitely prolong life in male patients who have had a myocardial infarct before the age of 50" appears in a circular letter recently sent to physicians by the manufacturer (Ayerst). The claim is based on a study reported at the January 25th meeting of the Western Section of the American Federation of Clinical Research by Dr. Jessie Marmorston and her associates.

Two synthetic estrogens, ethinyl estradiol (Lynoral - Organon) and mytatriendiol (Anvene - Searle), and a placebo were included in the study along with Premarin, but they were found to have no effect on survival. All of the patients in

the study were male, and the doses of the three estrogens were limited to amounts that caused tolerable breast soreness and enlargement.

The data presented show that only 50 patients were followed for more than nine months after they started taking Premarin; 40 of these were followed for more than 15 months, and only 18 for more than two years. Conclusions based on such a small series observed over such a short period can hardly give decisive results in a disease with such an unpredictable course and with so many unknown variables. Contrary to the implications of the manufacturer's statement, most of the patients in the study were not under 50, but were 60 to 80 years old.

When patients initially included died, all data relating to them were dropped from the study unless it was judged that they had died of atherosclerotic heart disease. Since autopsies were performed in only about 40 per cent of the fatalities, the possibility of mistaken diagnoses in the other 60 per cent cannot be ruled out. A few such mistakes could destroy the claimed statistical significance of the findings. Furthermore, the published results exclude all data on subjects who for whatever reason failed to complete 75 days of treatment. If some of these subjects died, the most vulnerable patients may have been eliminated from the study.

EFFECTS ON CHOLESTEROL - One of the reported findings is that Lynoral and Anvene did produce a significant change in the cholesterol-phospholipid ratio, while Premarin did not. This finding has little meaning. The time interval between the antecedent myocardial infarction and the subsequent blood sampling is not stated; and large spontaneous changes in serum lipids are known to occur in the few months after acute infarction. Furthermore, changes in body weight cause fluctuations in the lipids. The failure to account for these changes and the failure to establish a pre-treatment base line makes interpretations of subsequent changes in serum lipids questionable.

The rationale for the study of the relationship of estrogens to coronary artery disease arises from the fact that young men have this disease much more frequently than young women, with the difference between the sexes in the incidence of the disease diminishing strikingly after the menopause in women. It has also been noted that young women have lower levels of serum cholesterol and beta-lipoprotein and higher levels of alpha-lipoprotein than either young men or older men or women. However, the doses of estrogens required for a favorable effect on serum lipids and lipoproteins produce a degree of feminization which few men will tolerate.

It is possible that long-term treatment of coronary patients with estrogens might affect the course of the disease, as well as correct lipid abnormalities. Extensive studies by other investigators have as yet failed to establish such an effect, but further well-controlled studies over long periods of time with large numbers of patients are needed. Until improved survival with small doses of estrogens has been established, the physician must weigh a questionable benefit against such side effects, even with very small doses, as breast hypertrophy and discomfort, loss of libido, lassitude, inertia, anxiety, depression, and insomnia.

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